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10/698,599	10/31/2003	Joakim Wigstrom	58312 (47137)	5994

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EXAMINER	
NEGIN, RUSSELL SCOTT	
ART UNIT	PAPER NUMBER
1631	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/698,599	WIGSTROM ET AL.	
	Examiner	Art Unit	
	RUSSELL S. NEGIN	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 7-189* is/are pending in the application.

4a) Of the above claim(s) *7 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,8-34 and 36-189* is/are rejected.

7)☒ Claim(s) *166* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Comments

Applicants' amendments and request for reconsideration in the communication filed on 2 December 2008 are acknowledged and the amendments are entered.

Claims 7 and 35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10 April 2008.

Claims 1-3 and 7-189 are pending, and claims 1-3, 8-34, and 36-189 are examined in the instant Office action.

Withdrawn Objections/Rejections

The objections to claims 40, 57, 69, 75, 93, 123, 133, 145 and 152 because of informalities are withdrawn in view of amendments filed to the instant set of claims on 2 December 2008.

The rejections of claims 1, 8, 15-18, 24-25, 27, 38-39, 43-51, 54-57, 60-61, 67-73, 78-80, 85, 87-93, 100-102, 105, 107-117, 120-121, 124, 126, 131, 134, and 161 under 35 U.S.C. 102(b) as being anticipated by Klein et al. [US Patent 5,413,686; issued 9 May 1995; filed 17 July 1992] are withdrawn in view of amendments filed to the instant set of claims on 2 December 2008.

Claim Objections

Claim 166 is objected to because of the following informalities:

Line 1 of claim 166 misspells "microfluidic" as "microfluidc."

Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

<u>35 U.S.C 103 Rejection #1</u>:

Claims 1-3, 8-13, 15-18, 24-33, 36-39, 43-94, 97-98, 100-122, 124-134, 137-139, 142-149, 151, 153-155, and 159-161 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klein et al. in view of Agilent [Agilent capillary electrophoresis system; brochure; 12 pages; published 1 September 2001].

Claim 1 is drawn to a computer program product comprising a computer readable medium having computer readable program code embodied in the medium for causing an application program to execute on a computer, wherein the program product comprises instructions for controlling one or more functions of a microfluidic substrate in response to received data regarding one or more substrate properties.

Claim 2 is drawn to the same subject matter as instant claim 1 with the additional limitation of controlling one or more functions of a microfluidic substrate in response to received data regarding one or more properties of a sensor in fluid communication with at least one microchannel of the substrate.

Claims 1 and 2 are further limiting wherein the one or more function comprises sequentially exposing a cell based biosensor in electrical communication with an electrode to multiple fluid streams from one or more microchannels in the substrate by moving the sensor, moving the substrate, moving both the sensor and the substrate, and/or varying the pressure of one or more of the microchannels.

Claim 3 is drawn to a computer program product comprising a computer readable medium having computer readable program code embodied in the medium for causing an application program to execute on a computer, wherein the program product comprises instructions for controlling the exposure of a cell based biosensor to multiple

fluid streams from a plurality of outlets of more or microchannels in the substrate by varying the pressure of one or more of the microchannels.

Klein et al. teaches a multi-channel automated capillary electrophoresis analyzer.

Specifically, Figure 8 and column 10, lines 22-45 of Klein et al. teach the computerized limitations behind the capillary electrophoresis system. Specifically, this section teaches computer program product comprising a computer readable medium causing operation of the computer (in the case of Klein et al. the computer controlling the CE apparatus is an IBM with a floppy disk). The substrate in this instance is the capillary itself, and the properties being measured relate to flow of liquid through the capillary (see Figure 3 of Klein et al.).

However, Klein et al. does not teach scanning of sensors or instructions for controlling the scanning of sensors.

Agilent is a brochure describing the benefits of using an Agilent capillary electrophoresis system for measuring biomolecules. Specifically, the fourth page of the brochure measures the migration time of an oligonucleotide sensor. The brochure itself gives instructions for detecting sensors using the CE apparatus in the form of specifications on the penultimate page of the brochure. Pressure variance is illustrated on page eighth page of the brochure.

With regards to claim 5 and 103-104, the abstract of Klein et al. indicates the plurality of capillary substrates. The Agilent brochure indicates, as discussed above, movement of the sensor through the capillary. When buffer is delivered to each of the channels (as in Klein et al.), there is buffer delivered to each adjacent capillary (i.e. capillaries with sensors/agents).

With regards to claims 8, 15-16, and 87-88, Klein et al. illustrates movement of an aqueous liquid from a reservoir through the capillary into a second reservoir in Figure 3.

With regards to claims 17 and 89, Klein et al. is a capillary electrophoresis procedure that applies electric fields to capillaries [see abstract of Klein et al.]

With regards to claims 18 and 38, Klein et al. teaches the computerized limitations governing the electrophoresis in Figure 8 and column 10, lines 22-45 of Klein et al.

With regards to claims 24-25, 48-49, 51, 93, 100-101, and 105, Figure 6 of Klein et al. illustrates automated delivery of four fluids to the capillaries, including flow of buffer. The buffer includes ionic NaOH. This buffer is a component of the filled capillary.

With regards to claims 26, 52, 65, and 76, the fourth page of the Agilent brochure indicates the movement of oligonucleotide sensors and buffer through the capillary substrate in a continuous manner.

With regards to claims 27, 110, 114-117 and 121, the abstract indicates use of a vacuum to regulate pressure and help move liquid in the capillary channel.

With regards to claims 9-11 and 53, Figure 3 of Klein et al. illustrates a UV detector that scans near the output of the capillary substrate. The Agilent brochure indicates, as discussed above, movement of the sensor through the capillary. The figure on the fourth page of the Agilent brochure illustrates signal data.

With regards to claims 12-13, the fifth page of the Agilent brochure indicates the physiological response of the production of DNA and protein resulting from PCR hybridization reaction with PCR agents.

With regards to claims 28, 32-33 and 36-37, instructions for delivering agent/buffer to the capillary system are illustrated in the monitor on the second page of the Agilent brochure. The computer has a memory. The figure on the fourth page of the Agilent brochure illustrates response data.

With regards to claims 29-30, the abstract of Klein et al. teaches a plurality of capillaries and the fourth page of the Agilent brochure illustrates the result of delivery of an agent to a capillary substrate.

With regards to claim 31, the fourth page of the Agilent brochure indicates a change in amount of oligonucleotide added the capillary substrate (i.e. the intensities of each electropherogram differ depending on whether aqueous or organic solvent is used with the oligonucleotides).

With regards to claims 39, 50, 109 and 120, Klein et al. teaches modifications that cause temperature of the capillary to be adjusted in column 15, lines 46-55.

With regards to claims 43-47, 107-108 and 111-113, Figure 8 of Klein et al. teaches a processor in communication with a macroscale device that is in communication with a microfluidic device. Figure 8 also illustrates a power supply. This apparatus performs capillary electrophoresis using a voltage and a current to the substrate (i.e. a capillary channel).

With regards to claims 54-57, 60-61, 67-69, 73, 126, and 161 Figure 8 of Klein et al. illustrates a GUI in the form of a monitor that regulates and displays results of the CE in response to user commands and acquires, retrieves, and manages data from the CE

apparatus. Additionally, Figure 8 is viewed as a microfluidics workstation linked to a microfluidic substrate (i.e. the capillaries). Figure 8 also illustrates a memory board.

With regards to claim 58, the third page of the Agilent brochure indicates a linearity in the scanning process for capillary electrophoresis.

With regards to claim 59, the second page of the Agilent brochure indicates the presence of the sensor in the capillary.

With regards to claims 62-64, the fluids/sensor in the capillary substrate are scanned continuously at the detector window near the output of the capillary and the time of the sensor migration is recorded in the fourth page of the Agilent brochure. Consequently, the recorded property is the migration time.

With regards to claim 66, electropherograms of proteins are illustrated in the fifth page of the Agilent brochure.

With regards to claims 70-72 and 85, column 10, lines 58-64 of Klein et al. teaches use of an electrical current monitoring resistor to monitor and regulate current and voltage across the capillary substrate in response to feedback or a user or data acquisition system.

With regards to claim 74, the workstation illustrated on the second page of the brochure illustrates the instructions for performing the capillary electrophoresis.

With regards to claims 75 and 77, the ninth page of the Agilent brochure illustrates the CE-MS procedure with the MS abundances mapped to a database of biomolecular identifiers in the upper left corner of the figure on this ninth page with electropherograms.

With regards to claims 78-80, 90-92 and 131, the apparatus in Klein et al. is a macroscale device regulated by a power supply as illustrated in Figure 8 of Klein et al. and receives instructions from the computer. Furthermore, the electrical power supply illustrated in Figure 8 is regulated by the computer system to generate the desired electric field across the capillary.

With regards to claims 81-84 and 86, the second and third pages of the Agilent brochure illustrate a macroscale device comprising a detector for detecting response to a sensor in the form of signal data. The fourth page of the Agilent brochure illustrates a physiological response to oligonucleotides in which a mathematic operation is performed on the data after acquisition to generate the electropherogram.

With regards to claims 94 and 97-98, the electrophoresis apparatus in the third page of the Agilent brochure illustrates equipment in which an electric field applied to

capillary substrate containing a sensor. Specifically, the monitor on the third page of the Agilent brochure allows input data regarding the agent (i.e. amount of agent to be used).

With regards to claims 118-119 and 122, the fifth page of the Agilent brochure illustrates the separation of a group of proteins wherein the capillary substrate comprises the protein sensor.

With regards to claim 102, the abstract of Klein et al. teaches a plurality of substrates (i.e. capillaries) in the apparatus.

With regards to claim 124, Figure 3 of Klein et al. illustrates use of a UV light source to monitor the contents of the capillary.

With regards to claim 127-130 and 138, the computer on the third page of the Agilent brochure illustrates a graphical user interface with a substrate and apparatus properties and function parameters which include application of the electric field or vacuum. Additionally, a representation of a substrate is shown in the third page of the Agilent brochure.

With regards to claims 132-133, the sensor in the CE system comprises a memory (see third page of Agilent brochure and Figures 3 and 8 of Klein et al.)

recording the scanning data across fluid streams at a sensor location and sensor response as a function of time.

With regards to claim 134, the cover Figure of Klein et al. illustrates a circular stage for receiving substrate molecules that is rotatable in a circular (i.e. x and y directions).

With regards to claim 137, the mouse on the Agilent computer system is interpreted to be a joystick.

With regards to claim 139, the fourth page of the Agilent brochure illustrates a selection of and an operation of the abundance as a function of migration time of the sensor in the capillary under an applied electrical field.

Claim 142 is further limiting wherein the system further comprises a first computer program product according to any of claims 1-3, a second computer program product comprising computer program code from acquiring data relating to properties of a sensor in fluid communication with at least one channel of the microfluidic substrate; and a data processing system for accessing the data relating to properties of the sensor and for providing the data to the first computer program product.

Claim 143 is further limiting wherein the instructions executed by the first program product affects the second program product.

The patent of Klein et al. documents the first computer system in Figure 8 and column 10, lines 20-45. The Agilent brochure details a second computer system used to detect the presence of a sensor in the capillary substrate channel.

With regards to claim 144, Klein et al. teaches use of a vacuum to regulate pressure in the abstract.

Claim 145 is further limiting wherein a sensor in fluid communication with at least one microchannel on a microfluidic substrate;

--providing data to a computer program product according to any of claims 1-3, wherein in response to the data provided, the computer program product provides instructions to a scanning mechanism to execute one or more scanning functions such that the substrate, the sensor, or the substrate and the sensor move relative to one another, and/or such that pressure is altered in at least one microchannel of the substrate.

The fourth page of the Agilent brochure indicates the movement of oligonucleotide sensors and buffer through the capillary substrate in a continuous manner. The concentration of sensor varies with time as is measured when scanned by a UV detector proximate to the output of the capillary (see Figure 3 of Klein et al.). Additionally, Klein et al. describes a vacuum to regulate pressure in the capillary in the abstract.

With regards to claims 146 and 151, the capillary system in Agilent brochure (i.e. fourth page) indicates a fluid stream (i.e. buffer) with a sensor/agent (i.e. oligonucleotide) as a function of time.

With regards to claim 147, Klein et al. discloses an electrophoresis system with a plurality of capillary substrates. The Agilent brochure introduces sensors into the capillaries.

With regards to claims 148-149, Figure 6 of Klein et al. illustrates a pre-programmed set of four chemicals automatically inserted into the apparatus. The scans of sensors as a function of migration time are continuous and illustrated in the fourth page of the Agilent brochure.

With regards to claim 153-155 and 159, Figure 3 of Klein et al. and the abstract show the varying of pressure and the UV detection of the sensor (i.e. such as those disclosed in Agilent brochure) near the output of the capillary. The sensor is detected in response to UV light, and the flow of the surrounding fluid in the channel. The detection of the sensor is measured in response to an electrical field.

With regards to claim 160, the third page of the Agilent brochure illustrates a graphical user interface where there is data that is entered and the sensor is then scanned for optical properties.

It would have been to someone of ordinary skill in the art at the time of the instant invention to modify the capillary electrophoresis apparatus of Klein et al. by use of the sensors, agents, and capillary electrophoresis apparatus of the Agilent brochure wherein the motivation would have been that the use of a sensor gives the apparatus an entity with which to measure migration time [i.e. the Figure on the fourth page of Agilent]. Furthermore, the computer GUIs in Agilent provide a further means of automation to the apparatus of Klein et al. Furthermore, the multiple capillaries in the apparatus with the computer system of Klein et al. enable multiple experiments (i.e. of sensors such as those in computer system/apparatus of Agilent) to be performed at once.

Response to arguments:

Applicant's arguments filed 2 December 2008 have been fully considered but they are not persuasive.

Applicant first argues on page 38 of the Remarks that "nowhere is 'capillary electrophoresis' recited in the present claims. However, applicant also states on the same page of the Remarks:

> The presently claims device is not directed to a capillary electrophoretic device, ALTHOUGH THE CLAIMED DEVICE MAY BE ENVISIONED TO FURTHER INCLUDE A CAPILLARY ELECTROPHORETIC COMPONENT.

Applicant further argues on page 40 of the remarks that while all claims require a "cell-based biosensor," Klein et al. and Agilent do not teach or suggest cell-based biosensors.

As applicant states the definition of "cell based biosensor" on page 40 of the Remarks:

> As used herein, the term, “a cell-based biosensor" refers to an intact cell or **A PART OF AN INTACT CELL**… which is capable of providing a detectable physiological response upon sensing a condition in an aqueous environment in which the cell (**OR PART THEREOF**) is placed.

Consequently, applicant’s arguments are not persuasive because the DNA shown on the fifth page of the Agilent brochure fits this definition of a cell based biosensor.

Applicant argues on page 43 that:

> Nowhere does the Agilent brochure disclose or suggest the claimed invention in which a cell based biosensor is sequentially exposed to multiple fluid streams from one or more microchannels in a substrate by moving the sensor, moving the substrate, moving both the sensor and the substrate and/or by varying pressure of one or more of the microchannels.

This argument is not persuasive because while Agilent teaches use of biosensors, the invention of Klein et al. teaches a multi-channel automated capillary electrophoresis analyzer wherein the samples are analyzed in sequence as they move through the channels (i.e. capillaries) [see abstract and cover figure of Klein et al.]. Consequently, the combination of Klein et al. and Agilent teaches the limitations of the instantly rejected claims.

35 U.S.C. 103 Rejection #2:

Claims 14, 19-23, 99, and 156 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klein et al. in view of the Agilent brochure as applied to claims 1-3, 8-13, 15-18, 24-33, 36-39, 43-94, 97-98, 100-122, 124-134, 137-139, 142-149, 151, 153-155, and 159-161 above, and further in view of Colton et al. [Electrophoresis, 1998, volume 19, pages 367-382].

Claims 14, 19-20, 22 and 99 are further limiting comprising delivering an agent to a sensor.

Claim 21 is further limiting wherein a parameter of the agent comprises a property of the agent.

Claim 23 is further limiting wherein the data is dose-respondent.

Claim 156 is further limiting wherein the result is a different electrical charge for the sensor.

Klein et al. and Agilent make obvious a capillary electrophoresis system for detecting the presence and properties of sensors and analytes, as discussed above.

Klein et al. and Agilent do not describe interactions between the sensor and analyte in the capillary substrate.

The review of Colton et al. studies the technique of affinity capillary electrophoresis, which as illustrated in Figure 1 on page 369 shows how capillary electrophoresis is able to measure the binding constant between a receptor (i.e. sensor) and a ligand (i.e. agent) by comparing the migration times of the receptor, ligand, and receptor-ligand complex. Figure 1 also illustrates that an electrical property (i.e. the charge) changes as a result of complex formation.

It would have been obvious someone of ordinary skill in the art at the time of the instant invention to modify the capillary electrophoresis apparatus of Klein et al. and Agilent by use of the affinity capillary electrophoresis of Colton et al. wherein the

motivation would have been that by combining binding affinities (i.e. of agents relative to sensors) with capillary electrophoresis, a more advanced means for determining binding constants of physiologically relevant processes is developed [see introduction on pages 367-368 of Colton et al.].

Response to arguments:

Applicant's arguments filed 2 December 2008 have been fully considered but they are not persuasive.

Applicant argues that since the combination of Klein et al. and Agilent is allegedly deficient, the instant rejection is also deficient. Since this combination of references is not deficient, the instant rejection is maintained.

35 U.S.C. 103 Rejection #3:

Claims 34, 40-42, 150, and 152 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klein et al. in view of the Agilent brochure as applied to claims 1-3, 8-13, 15-18, 24-33, 36-39, 43-94, 97-98, 100-122, 124-134, 137-139, 142-149, 151, 153-155, and 159-161 above, and further in view of Katayama et al. [Analytical Chemistry, 1998, volume 70, pages 2254-2260].

Claim 34 is further limiting wherein sensors are superfused at different time intervals according to instructions from the computer readable media.

Claim 40 is further limiting wherein the parameters are alters for the one or more functions in response to a measured condition of the microfluidic substrate or sensor.

Claim 41 is further limiting wherein the measured condition comprises an electrophoresis event.

Claim 42 is further limiting wherein the substrate function comprises time to complete scanning.

Claim 150 is further limiting wherein the sensor is paused during a given time interval.

Claim 152 is further limiting wherein he fluid streams provide interdigitating fluid streams of agent and buffer and the sensor is sequentially scanned across the fluid streams.

Klein et al. and Agilent make obvious a capillary electrophoresis system for detecting the presence and properties of sensors and analytes, as discussed above.

Klein et al. and Agilent do not teach superfusing, interdigitating, altering in response to a property of a sensor, or pausing during an electrophoresis run.

The study of Katayama et al. studies stable capillary coating with successive multiple ionic polymer layers. The "Procedure of SMIL coating" as taught in the paragraph bridging columns 1 and 2 of page 2255 includes pauses before each injection with buffered agents/sensors. Consequently, each layer is superfused at

different time intervals (i.e. see Figure 1 on page 2255 of Katayama et al.). The electrophoresis event being modified by successively (i.e. interdigitating) coating the capillary with ionic layers is to change in direction of the electroosmotic flow (again, see Figure 1 of page 2255 of Katayama et al.). Time to complete scanning is shown in Figure 5 of Katayama et al.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the capillary electrophoresis apparatus of Klein et al. and Agilent by use of the SMIL capillary coating procedure of Katayama et al. wherein the motivation would have been that the modifications (i.e. interdigitating, pausing) would have allowed a more advanced, regulated electrophoresis process with less interaction between the sensor/agent and the wall of the capillary [see for example, introduction on page 2254 of Katayama et al.]

Response to arguments:

Applicant's arguments filed 2 December 2008 have been fully considered but they are not persuasive.

Applicant argues that since the combination of Klein et al. and Agilent is allegedly deficient, the instant rejection is also deficient. Since this combination of references is not deficient, the instant rejection is maintained.

35 U.S.C. 103 Rejection #4:

Claims 95-96, 123, 135-136, 140-141, 157-158, and 162-189 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klein et al. in view of the Agilent brochure as applied to claims 1-3, 8-13, 15-18, 24-33, 36-39, 43-94, 97-98, 100-122, 124-134, 137-139, 142-149, 151, 153-155, and 159-161 above, and further in view of Jardemark et al. [Analytical Chemistry, 1997, volume 69, pages 3427-3434].

Claim 95-96 are further limiting wherein the electric field can electroporate a membrane of the cell structure.

Claims 123 and 157 are further limiting wherein the sensor comprises a cell or cell fraction.

Claims 135, 140, and 158 are further limiting wherein the workstation or program suite comprises executing patch clamp analysis. Claim 141 is further limiting comprising computer code for analyzing patch clamp data.

Claim 136 is further limiting comprising mechanisms for controlling movement of the stage.

Claims 162-189 are drawn to a computer program product and system that utilize a patch clamp system and pressure (negative and positive) to introduce cell based biosensors into a plurality of microchannels in communication with electrodes that then generate electric fields through these microchannels. Claims 162-189 comprise a plurality of reservoirs (i.e. chambers) used to hold the cell based biosensors before and after electrophoretic analysis. The cell based biosensors are SEQUENTIALLY exposed to a plurality of fluid streams from one or more microchannels.

Klein et al. and Agilent make obvious a capillary electrophoresis system (including computer code and computer readable media) for detecting the presence and properties of sensors and analytes, as discussed above.

Klein et al. and Agilent do not teach use of cells and patch clamp analysis.

The study of Jardemark et al. studies patch clamp detection in capillary electrophoresis.

Specifically, Figure 1 on page 3429 of Jardemark et al. illustrates the patch clamp procedure with the cellular components undergoing electrophoresis (i.e. the sensor comprises fragments of the cells). The caption of Figure 1 indicates that the setup is capable of being manipulated with "micromanipulators."

Claim 162 is drawn to a computer program product comprising:

--a computer readable medium having computer readable program code embodied in the medium for causing an application program to execute on a computer, wherein the program product comprises instructions for controlling a fluid delivery control mechanism;

--delivers a cell based biosensor via a fluid through a first microchannel in a microfluidic substrate to a sensor chamber comprising one or more electrodes in communication with a sensor chamber which form a patch clamp system;

--applies a negative pressure to a second microchannel so as to position said cell based biosensor in electrical communication with the one or more electrodes;

--sequentially exposes the cell based biosensor to a plurality of fluid streams from one or more microchannels.

As discussed above, Klein et al. and Agilent teach a computer readable medium in a computer product causing controlled fluid delivery of a cell based biosensor (i.e. DNA) using a plurality of electrodes [i.e. see cover Figure of Klein et al.] Negative pressure (i.e. a vacuum) to the microchannel initiates positioning of the DNA in the microchannel. Klein et al. describes this process for a plurality of capillaries in

sequence [see Figure 2 of Klein et al.] Klein et al. and Agilent do not show a patch clamp system.

As discussed above. the study of Jardemark et al. studies patch clamp detection in capillary electrophoresis.

Specifically, Figure 1 on page 3429 of Jardemark et al. illustrates the patch clamp procedure with the cellular components undergoing electrophoresis (i.e. the sensor comprises fragments of the cells). The caption of Figure 1 indicates that the setup is capable of being manipulated with "micromanipulators."

With regards to claims 163-165, Figure 8 of Klein et al. illustrates computer program products for acquiring data from a plurality of microchannels in the electrophoresis apparatus. Additionally, Figures 6 and 8 of Klein et al. illustrate the data acquisition system operably linked to a microfluidic substrate.

With regards to claim 166, Figure 3 of Klein et al. illustrates a microfluidic substrate comprising a microchannel in communication with sensor chambers comprising electrodes.

With regards to claim 167, Figure 1 of Jardemark et al. illustrates an in chip patch clamp detection system for capillary electrophoresis.

With regards to claims 168-169, Figures 6 and 8 of Klein et al. illustrate a means for providing data to alter the substrate functions.

With regards to claim 170, Figure 3 of Klein et al. illustrates application of an electric field across an electrically conducting surface (i.e. a capillary) which contains the biosensor.

With regards to claims 171-172, the caption of Figure 1 of Jardemark et al. indicates that the patch-clamp setup is capable of being manipulated with "micromanipulators" capable of fragmenting cell membranes.

With regards to claims 173-174 and 177, Figures 3, 6, and 8 of Klein et al. illustrate a computer program product for using a computer to input data relating to the electric field properties of the system that comprises using the detector of Figure 3 of Klein et al.

With regards to claim 175-176, page 5 of Agilent illustrates the input to the detector regarding the product of a PCR (i.e. hybridization) reaction of DNA.

With regards to claim 178, the capillary electrophoresis device in Figure 3 of Klein et al. exposes the sensor (i.e. the DNA of Agilent) to an electric field.

With regards to claim 179-180, Figure 8 of Klein et al. illustrates a data acquisition system that inputs data relating to properties of the electric field. Figure 8 of Klein et al. also illustrates a power supply (label 670) for controlling power to the system.

With regards to claims 181-183, Figures 6 and 8 of Klein et al. illustrate use of a computer program product to control delivery through a channel of a substrate. Page 5 of Agilent further illustrates delivery of a plurality of agents to the sensors in a system such as in Figures 6 and 8 of Klein et al. The cover Figure of Klein et al. illustrates a plurality of reservoirs to apply to cell based biosensors.

With regards to claims 185-188, Figure 8 of Klein et al., label 510 shows use of a vacuum pump while the eighth page of Agilent illustrates a positive pressure profile within a capillary substrate. Figure 1 of Jardemark et al. illustrates a microfluidic chip that contains samples and buffers in communication with a microchannel in communication with a waste reservoir.

With regards to claims 189, Figure 3 of Klein et al. illustrates a fluid delivery mechanism delivering two or more substantially separate fluid streams through a microchannel (i.e. see pages 4-5 and Agilent for examples of such separate fluid streams).

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the capillary electrophoresis apparatus of Klein et al. and Agilent by use of the patch clamp capillary electrophoresis apparatus of Jardemark et al. wherein the motivation would have been that this patch clamp method on cells is useful in fractionating biological tissues and can sense very low concentration and small-sized analytes (see penultimate paragraph of the introduction on page 3428 of Jardemark et al.). It would have been further obvious to apply the pressures (positive and negative) and waste collection of Klein et al. to the microfluidic device of Jardemark et al. wherein the motivation would have been that such pressures and waste collections permit more convenient analyses of the cell based biosensors [see Figure 1 and its caption in Jardemark et al.]

Response to arguments:

Applicant's arguments filed 2 December 2008 have been fully considered but they are not persuasive.

Applicant argues that since the combination of Klein et al. and Agilent is allegedly deficient, the instant rejection is also deficient. Since this combination of references is not deficient, the instant rejection is maintained.

Applicant additionally argues that the motivation and reasonable expectation of success in combining Jardemark et al. with the instantly rejected claims is also deficient. The motivation is stated above and reiterated:

> It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the capillary electrophoresis apparatus of Klein et al. and Agilent by use of the patch clamp capillary electrophoresis apparatus of Jardemark et al. wherein the motivation would

have been that this patch clamp method on cells is useful in fractionating biological tissues and can sense very low concentration and small-sized analytes (see penultimate paragraph of the introduction on page 3428 of Jardemark et al.).

Consequently, there would have been a reasonable expectation for success in combining these references because the electrophoretic methods of Klein et al. and Agilent are generally applicable to the specific cells and patches of Jardemark et al.

35 U.S.C. 103 Rejection #5:

Claim 125 is rejected under 35 U.S.C. 103(a) as being unpatentable over Klein et al. in view of the Agilent brochure as applied to claims 1-3, 8-13, 15-18, 24-33, 36-39, 43-94, 97-98, 100-122, 124-134, 137-139, 142-149, 151, 153-155, and 159-161 above, and further in view of Couderc et al. [Electrophoresis, 1998, volume 19, pages 2777-2790].

Claim 125 is further limiting wherein the light source is a laser in optical communication with a sensor in a microchannel.

Klein et al. and Agilent make obvious a capillary electrophoresis system for detecting the presence and properties of sensors and analytes, as discussed above.

Klein et al. and Agilent do not teach use of a laser in optical communication with a sensor.

The study of Couderc et al. teaches a CE apparatus with a laser induced fluorescence detector (see abstract of Couderc et al.)

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the capillary electrophoresis apparatus of Klein et al. and

Agilent by use of the LIF detector in Couderc et al. wherein the motivation would have been that using such a detector allows greater sensitivity and as a result less sensor amount (see introduction on page 2777 of Couderc et al.).

Response to arguments:

Applicant's arguments filed 2 December 2008 have been fully considered but they are not persuasive.

Applicant argues that since the combination of Klein et al. and Agilent is allegedly deficient, the instant rejection is also deficient. Since this combination of references is not deficient, the instant rejection is maintained.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Marjorie Moran, Supervisory Patent Examiner, can be reached at (571) 272-0720.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only.

For more information on the PAIR system, contact the Electronic Business Center

(EBC) at 866-217-9197 (toll-free).

/RSN/
Russell S. Negin
23 February 2009

/Marjorie Moran/
Supervisory Patent Examiner, Art Unit 1631